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Review Article

Primary Adrenal Lymphoma: When the Attempt to Cure Becomes the Way to Make Diagnosis. Case Report and Systematic Review of the Literature

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Abstract

Sometimes, in clinical practice, making the correct diagnosis can be very hard: adrenal masses are an example of these conditions. Among Differential Diagnosis (DD), there is Primary Adrenal Lymphoma (PAL), a rare condition with very poor prognosis. In this review, PAL main features (patient characteristics, symptoms, laboratory and imaging findings, pathogenesis, histological features, prognosis and prognostic factors and treatment) that have been reported in the English literature since September 2017 are analysed. We also report a case of PAL diagnosed with laparoscopic adrenalectomy and treated with R-CHOP chemotherapy, with a complete response at over 10-year follow-up.

Keywords: Adrenal Tumours; Diffuse Large B-Cell Non-Hodgkin Lymphoma; Laparoscopic Adrenalectomy; Primary Adrenal Lymphoma

List of Abbreviations

DD	:	Differential Diagnosis
PAL	:	Primary Adrenal Lymphoma
R-CHOP	:	Rituximab Cyclophosphamide Doxorubicin Vincristine Prednisolone
NHL	:	Non Hodgkin Lymphoma
GRADE	:	Grading of Recommendations Assessment Development and Evaluation
RCT	:	Randomized Clinical Trial
CT	:	Computed Tomography
MRI	:	Magnetic Resonance Imaging
CBC	:	Complete Blood Count
ESR	:	Erythrocyte Sedimentation Rate
CRP	:	C-Reactive Protein

WHO	:	World Health Organization
PET	:	Positron Emission Tomography
CNS	:	Central Nervous System
LDH	:	Lactate Dehydrogenase
FDG	:	Fludeoxyglucose
HIV	:	Human Immunodeficiency Virus
EBV	:	Epstein-Barr Virus
DLBCL	:	Diffuse Large B Cell Lymphoma
LA	:	Laparoscopic Adrenalectomy

Introduction

Primary Adrenal Lymphoma (PAL) is a rare condition with less than 200 cases described in the English literature. Although secondary adrenal involvement as a part of disseminated lymphoma is common, occurring in 25% of patients affected by Non-Hodgkin's Lymphomas (NHLs), PAL instead occurs in less than 1% of NHL cases [1].

Therefore, it is difficult to define the features of this disease exactly. From small case series and case reports, PAL was more frequent in elderly men and patients often report to suffer from B-symptoms, pain and fatigue. The majority of cases of PAL are bilateral and they can produce absolute or relative adrenal insufficiency [2]. Histologically, diffuse Large-B-cell lymphoma is the most frequent type of PAL [3]. A correct diagnosis is essential to establish a proper treatment, nonetheless, it is often very difficult to make a diagnosis and this aspect affects the prognosis.

The prognosis is poor and a prolonged disease-free survival appears rare, in fact, most of these tumours are highly aggressive and their treatment cannot be satisfactory [2,4]. Therapeutic strategies include surgery, combination chemotherapy and/or radiotherapy [3]. In this review, PAL's main features that have been reported in the English literature since September 2017 are analyzed. The case of a patient affected by a tumour of unknown origin, located in the right adrenal gland and laparoscopically resected, that resulted to be PAL after pathological examination and that was successively treated with a specific chemotherapy is also discussed.

Methods

The methodological approach consisted of: identification of the selection criteria, definition of the search strategy, assessment of the study quality, and extraction of the relevant data, according to the PRISMA statement checklist for developing a systematic review [5]. The study selection criteria were defined before starting the data collection in order to allow the proper identification of the eligible studies for the analysis.

A literature search was performed using MEDLINE (through PubMed), EMBASE, and Google Scholar, using the key words "Primary adrenal lymphoma''. The final search was completed on the 31st September 2017. Comparative and non-comparative studies, case reports and retrospective series reporting new cases of PAL have been included in this report, regardless of their size. All titles and abstracts were assessed by two independent reviewers (MM, LM) to select those focusing on PAL and its treatment. Full-text of the selected trials were screened by the authors for eligibility. Reference lists of all the relevant articles were screened in order to identify additional articles that could have been potentially useful for the purposes of this study.

The following inclusion criteria have been used:

- Acknowledged as an original article.
- Full-text published in English. Some limits were established, for example "species: humans".

The following variables were extracted from each study: patients' features (age at initial diagnosis, gender, geographical origin), presenting symptoms, laboratory and imaging findings, pathogenesis, histological features, prognosis, prognostic factors and treatment. Any disagreement between the two reviewers during the study selection process was resolved following discussion with a third reviewer (CLB). The Grading of Recommendations Assessment Development and Evaluation (GRADE) system was used to grade the "body of evidence" emerging from this review [6].

Results

The preliminary literature search identified 457 articles. 281 were rejected because they were not pertinent to the review questions, and 40 were excluded because they were not in English. 136 articles were retained after screening their titles and abstracts. At the full-text examination, 11 articles were excluded (6 because they were review articles not reporting new cases of PAL, 3 because the abstract was not available and 2 because reporting duplicated data from the same institution with clear overlap). Eventually, 125 articles were selected. The manual search and the crosscheck of the reference lists did not produce any other relevant article. A flow chart illustrating the study identification and inclusion/exclusion processes is shown in Figure 1.

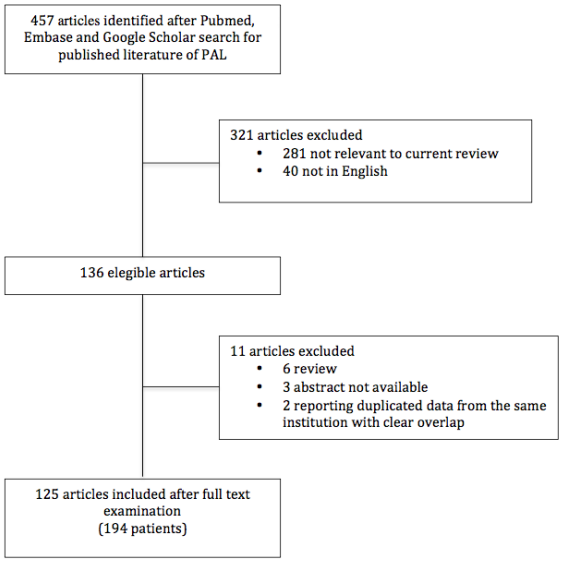

Figure 1: Flowchart of systematic review.

The methodological quality of the included studies was scored according to GRADE system. No RCT was found; the included studies were significantly heterogeneous in their design, aims and methods. Among the 125 selected studies 15 were case series and 110 were case reports, reporting of a total of 194 patients with PAL (122 males and 53 women; 19 not available).

The GRADE system was used to enable a consistent judgment of the quality of the available evidence included in this systematic review, and the studies retrieved were judged as having evidence of very low quality. Selected studies were performed in heterogeneous populations: 64 in Asian, 35 in European, 21 in Northern American, 3 in Australian and 2 in African patients.

The main epidemiological and clinical features of patients, resulted from the literature review, are reported in Table 1. The main pathological, diagnostic and therapeutic data regarding of PALs, resulted from the literature review, are reported in Table 2.

Category	No (%) or median(range)
Gender	
M/F	122 (62.9)/ 53 (27.3)
NA	19 (9.8)
Demographic features	
Asiatic	98 (50.5)
European	70 (36.1)
Northern American	21 (10.8)
African	3 (1.55)
Australian	2 (1.03)
Presenting symptoms	
·Symptomatic	112 (57.7)
- Fever	48
- Abdominal pain	37
- Weight loss	51
- Nausea	13
- Asthenia	14
- Anorexia	16
- Fatigue	24
-Vomiting	11
·Asymptomatic (incidentaloma)	23 (11.8)
· NA	59 (30.4)
Median age*	61 (17-84)
Data are reported as number of patients and percentage in brackets. *Data are reported as years and range in brackets. M: Males; F: Females; NA: Not Available.	

Table 1: Epidemiological, clinical, and diagnostic features of patients.

Category	No (%) or median(range)
Side of the PAL	
Bilateral	137 (70.6)
Monolateral	36 (18.5)
-Left	24
-Right	12
NA	21 (10.8)
PAL type at pathological examination	
B	163 (84)
T/NK	20 (10.3)
Mixed	1 (0.5)
NA	10 (5.15)
Diagnosis	
Radiological	
-Ce CT scan	99 (51.03)
-MRI scan	10 (5.15)
-18-FDG PET scan	10 (5.15)
-Ce CT + 18-FDG PET scan	39 (20)
-Ce CT + MRI scan	13 (6.7)
-Ce CT + 18-FDG PET scan +MRI	7 (3.6)
-MRI + 18-FDG PET scan	1 (0.5)
-NA	15 (7.7)
Histological	
- Percutaneous FNA biopsy	117 (60.3)
-Surgery	60 (30.9)

-NA	17 (8.7)
Median age*	61 (17-84)

Data are reported as number of patients and percentage in brackets.

NA: Not Available; PAL: Primary Adrenal Lymphoma; NK: Natural Killer; Ce CT: Contrast-Enhanced Computed Tomography; MRI: Magnetic Risonance Imaging; 18-FDG PET: 18 Fluorodeoxyglucose Positron Emission Tomography; FNA: Fine Needle Aspiration; CHOP: Rituximab Cyslophosphamide Doxorubicin Vincristine Prednisolone; R-CHOP: Rituximab Cyslophosphamide Doxorubicin Vincristine Prednisolone.

* 8 patients underwent more than one treatment

Table 2: Clinical, pathological, diagnostic and therapeutic data regarding PALs.

Case Report

A 65 years old man came to our attention because he has suffered from fatigue, fever and dry cough for a couple of months; he has taken antibiotics but has not recover. He has reported a history of hypertension for twenty years, well-treated with ACE-inhibitor and calcium-antagonist; in addition, he underwent two pancolonoscopies with endoscopic removal of two benign tumours of the colon; he has complained of diverticular disease of sigmoid colon. The clinical examination has not found masses in the neck neither in the abdomen. After a chest X-ray without abnormality, he performed a contrast-enhanced Computed Tomography (CT) scan of neck, thorax and abdomen that showed a right adrenal enlargement of hypo dense tissue with contrast enhancement, measuring 35 mm in diameter. This evidence was confirmed by a Magnetic Resonance Imaging (MRI) of the abdomen (Figure 2) that showed right homogeneous adrenal mass, which measured 50 mm x 27 mm, with hypo intense signal on T1 and mild hyper intense signal in T2 weighted images.

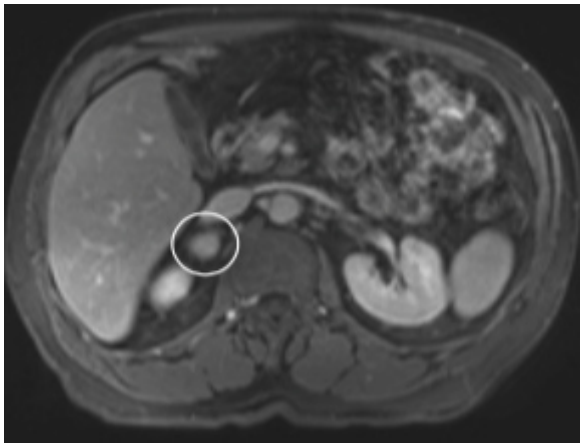

Figure 2: MRI scan of the abdomen showing right adrenal mass (50 mm x 27 mm).

Initial laboratory findings revealed a normal Complete Blood Count (CBC) except for mild anaemia (haemoglobin concentration of 10 g/dl), normal Erythrocyte Sedimentation Rate (ESR) and normal C-Reactive Protein (CRP). A serum biochemistry profile was within normal limits. Endocrinological examinations including plasmatic and urinary cortisol levels, plasmatic aldosterone in supine and hortostatic position, plasmatic renin activity in supine position, plasmatic epinephrine at rest, plasmatic norepinephrine at rest, urinary free cortisol, urinary 17-hydroxycorticosteroids, urinary vanillylmandelic acid were all within normal range.

After finding non-functioning right adrenal mass, without signs of infiltration of adjacent organs, a laparoscopic trans peritoneal right adrenalectomy was performed on July 2006 for a suspected pheocromocytoma. Operative time was 90 minutes with irrelevant blood loss. Postoperative course was uneventful. The patient resumed oral intake the day after the operation and was discharged by our hospital on the fourth postoperative day. An adrenal intravascular large B cells NHL (according to World Health Organization WHO 2001) resulted after histological examination. Immunostains: CD20+, CD79+, Bcl6+, CD3-, CD30-, ALK-, EBV-, CD138-, CD10-, MPO-, CK-. MIB1: 90%. Immunohistochemical analysis for CD31 showed specific intravascular localization of malignant cells.

After the unexpected diagnosis, the patient underwent a full lymphoma workup. Whole body PET-CT scan imaging was negative, except for a little subglissonian lesion, situated in the sixth hepatic segment, not detected on the previous MRI. Bone marrow aspirate and biopsy were also negative for malignancy. Serum biochemistry, including plasmatic Lactate Dehydrogenase (LDH) and beta2 macroglobulin, rachicentesis, bone marrow aspirate and biopsy were within normal limits.

The patient was treated with systemic chemotherapy using dose-adjusted R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine and Prednisone), and he underwent Central Nervous System (CNS) prophylaxis according to the literature [4]. After 12 cycles, there was no evidence of disease and the hepatic lesion disappeared. Every 6 months, the patient underwent haematological follow-up without recurrence of disease. On December 2013, he underwent open repair for right inguinal hernia. He is nowadays disease-free, after a follow-up of over 10 years.

Discussion

Adrenal masses of unknown origin represent a rather common problem in the clinical practice. Making a strict diagnosis, due to the lack of pathognomonic radiological features in lots of situations, and to the contraindication to perform fine needle biopsy in presence of non-functioning adrenal neoplasms [7] is often difficult. A correct and early diagnosis is mandatory in

order to start an accurate treatment. Unfortunately, preoperative differentiation between adrenal masses is still a big problem, in particular in the case of potentially malignant adrenal tumours. Among these masses, we have to keep in mind: pheocromocytomas, tuberculosis, histoplasmosis, cryptococcosis, metastatic tumours, adrenocortical tumours, adrenal hemorrages, PALs. PAL is a rare disease with fewer than 200 cases described in the English literature until September 2017 [2]; all the cases are reported as case report [3,8-116], case series [117-127], letter to the editor [128,129] and retrospective studies [130].

Although the incidence of secondary adrenal involvement, detectable on CT scan, is 5% [2] and autopsy studies demonstrated that 25% of the patients with NHL have involvement of the adrenal glands during the course of their disease, extra nodal malignant lymphomas originating from the endocrine glands occur only in 3% of cases [117]. Due to the rarity of the disease, there are poor data on PAL features with lack of strict definition. Recently, a definition was adopted from Rahidi et al according to a review of the literature; the authors defined PAL as an histologically proven lymphoma that involves one or both adrenal glands, in patients without prior history of lymphoma; if lymph nodes or other organs are involved, adrenal lesions have to be unequivocally dominant [2]. PAL is more frequent in middle age, with a median age at diagnosis of 61years (range 17-84) [3,8,9,11-50,52-56, 58-81,83-85,87-90,93-111,113,115,116,118-122,124-131], in males (M:F 2.3:1) [3,8,9,11-50,52-56,58-81,83-85, 87-90,93-111,113,115,116,118-122,124,126-131] and in eastern country.

Most frequently, presenting symptoms include B-symptoms, pain, and fatigue; nonetheless, anorexia, nausea and vomiting, neurological symptoms and diarrhea may occur as well [3,8,9,11,12,14-19,21, 23-25,27-30,32-36,38-40,42,43,45,47,52-56,61-71,73-75,77,79-81,83-85,88,90,93-96,98-102,106,107,109,111,113,119-122,125, 126,128,129,132]. In some cases, PAL can be diagnosed incidentally, without presenting symptoms [13,21,22,26, 31,37,41,44,46,48-50,59,60,72,76,87,89,97,103-105,108,116].

Skin/mucosal hyperpigmentation, hepatosplenomegaly and lymphadenopathy, hypotension and Addison's disease have been reported in the literature [2]. Usually PAL has bilateral involvement (70,6%) [8-12,14,15,17,20,21,23-26,28,29,31,32,34,35,39,41,44-46,50-56,58-70,73-75,77-80,83,84,86,87,89-96,98-102,105,106,108 113,115,118-122,124-126,128-131,133], only in 18,5% of cases it is mono-lateral with right-side and left-side localization of 33% and 67% respectively [13,16,18,19,22,27,30,33,36-38,40,42,47-49,71,72,76,81,85,88,97, 103,104,107,116,118,120,125,131,134].

The median maximum diameter at the time of diagnosis is of 8 cm (rang e 4-17) [65]. The most frequent laboratory finding is an elevated serum level of LDH**;** in some cases, PAL can produce absolute or relative adrenal insufficiency through unknown physio pathological mechanism [2]. Contrast-enhanced CT scan is the most appropriate imaging exam; PAL frequently appears hypo dense and with slight to moderate enhancement [114, 135]. The MRI scan may be useful in ambiguous cases; at the MRI scan, PAL usually appears iso/hypo intense in T1 and hyper intense in T2. At the 18-FDG PET and PET-CT scans, PAL shows an increased glucose uptake revealing a high metabolic activity [2].

In conclusion, when imaging findings indicate adrenal malignant lesions (size, density, intensity, and FDG uptake) PAL should be included in the differential diagnosis. The pathogenesis of PAL is unknown; an immune dysfunction seems to be the most important pathogenic factor implicated, considering that human adrenal glands usually do not contain any lymphoid tissue [2]. Other pathogenic factors that appear to be involved are mutations in the p53 and c-kit genes, HIV and EBV infection, concurrent or past history of cancer [65,135,136].

At pathological examination, B-cell type is the most common type of PAL, however, some cases of T-cell type lymphoma were also reported. In particular, diffuse large B-cell type accounts for more than 70% of cases of PAL; less common types are the small-cell, the mixed small and large-cell, and the undifferentiated lymphoma [3]. Majority of PALs are CD45 and CD20 positive at the Immunohistochemistry (IHC), and this may help in differential diagnosis.

Prognosis is usually poor, with a 20% 1-year survival [2]. The rate of CNS involvement is 2.2-5%, but in some cases it reaches 10% [4] and it seems to worsen long term prognosis [2]. There are various negative prognostic factors associated with a poor prognosis: old age, initial presentation with primary adrenal insufficiency, huge tumor size, elevated LDH level and involvement of other organs [4,131], but seems that the adrenal insufficiency is the most important one [131]. Anyway, the administration of systemic chemotherapy most of all influences the prognosis. In fact, as reported in a recent review, the mean duration of survival in patients treated with chemotherapy was 32-34 months, compared with 3.6-3.9 months in patients without response to chemotherapy [78]. In this regard, the case that we reported appeared different in many aspects from the majority of PALs reported in literature; our patient resulted disease free at 10-year follow-up. Treatment options for PAL include surgery, combination chemotherapy, surgery followed by chemotherapy and radiotherapy [3].

Chemotherapy seems the mainstay of treatment [49]; although the rarity of PAL and the lack of specific therapy, chemotherapeutic regimen similar to those used for other types of lymphomas are employed [117]. The largest study to date [4] stated that R-CHOP combination chemotherapy is an effective first-line regimen for primary adrenal DLBCL; on the other hand, it did not demonstrate any survival benefit in patients who underwent adrenalectomy

prior to chemotherapy. Moreover, R-CHOP seems to achieve the best improvement possible in terms of CNS relapse [117].

In a recent review [2] on univariate analysis, administration of chemotherapy added to surgery, but not radiation therapy, resulted significantly associated with longer survival. However, in multivariate logistic regression analysis, only administration of chemotherapy was significant predictor of outcome between therapeutic strategies. Although advanced age, adrenal insufficiency at onset, tumour size, LDH level and involvement of other organs have been reported as poor prognostic indicators [2,117]. The administration of systemic chemotherapy and the association with adrenal insufficiency were demonstrated to be the only prognostic factors. The role of the surgery in the management of adrenal masses is double: in rare cases [136] it is considered as a curative option, but in the majority of cases, as happens in NHL, it allows to make a correct diagnosis.

Indeed, pathological diagnosis by fine needle biopsy is usually not indicated for adrenal masses because of the risk of spreading cancer cells in adrenocortical cancer, as well as the low negative predictive value of this biopsy. On the other hand, clinical and radiological examination often fail to make a diagnosis [7]. Since its introduction in the surgical practice in 1992, surgeons have successfully expanded the indications of Laparoscopic Adrenalectomy (LA). Although the concerns of spreading and disseminating malignant cells into the abdominal cavity during manipulation of the tumours, it can actually be performed safely for monolateral and bilateral disease even treating malignants [137]. The literature has also showed that LA decreases morbidity, reduces length of hospitalization, reduces blood loss and analgesic requirement, and improves cosmesis compared to open adrenalectomy [7,138].

The case that we reported is consistent with the majority of the data reported in the literature for the clinical and diagnostic findings, with the exception of a normal level of LDH that was observed in our case, but it quite differs from the majority of PALs because it was monolateral and it had a particular pathological aspect due to its intravascular localization. Especially, it had a very good prognosis with complete response to the chemotherapy (12 cycles of R-CHOP) and the patient is actually disease free (follow-up over 10 years).

In this case, laparoscopic trans peritoneal right adrenalectomy was performed; this approach gave to the patient all the advantages of laparoscopic technique. We noticed, according to the literature, that this approach could be particularly useful in the treatment of adrenal masses of undetermined origin, irrespective of the size, keep firmly in mind the principles of en-bloc resection of all epinephric fat, and no touch technique [6].

Conclusion

In our experience, a correct surgical approach associated with R-CHOP chemotherapy was believed to be a good therapeutic option for PAL.

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